SST CORPORATION
635 Brighton Road (P.O. Box 1649)
Clifton, NJ 07015-1649
(973) 473-4300
FAX: (973) 473-4326
www.sst-corp.com

July 1, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Guidance for Industry; Drug Substance; Chemistry, Manufacturing and Controls Information (January 2004)

Docket No. 2003D-0571

Division of Dockets Management,

Thank you for the opportunity to comment on the subject Draft Guidance. Please note that these comments are being submitted by me as an individual and do not necessarily represent the views of my employer (SST Corporation) or of the numerous, worldwide API manufactures SST represents.

The following comments are exclusively focused on Attachments I and II of the Draft. These address the issue of identifying the starting material for the synthesis of a drug substance, whether prepared synthetically or derived from a biological source.

In general, the Draft provides a useful, novel and creative approach to the subject of identifying the starting material. What follows is a critique of the Draft and alternate suggestions to improve it.

1. Whether or not a starting material candidate (SMC) possesses a significant non-pharmaceutical market (lines 1689-1690), is not appropriate for determining its extent of documentation, nor to conclude whether the SMC is, in fact, the starting material. The proposed marketing-based criterion is confusing, unnecessary and not science-based.

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It is confusing, since by its nature it discusses the presence or absence of a negative, i.e., a *non*-pharmaceutical market (NPM). Double negatives are intrinsically confusing, i.e., molecules that do *not* have a *non*-pharmaceutical market. Further, the Draft could be interpreted as implying that if a molecule is without a significant NPM, then the molecule must have a significant Pharmaceutical market. This is not necessarily true, as the molecule could be a specialty, flavor or fragrance chemical.

It is unnecessary because there are more relevant criteria that could be employed (see discussion below) for determining the extent of documentation required and to support the decision as to what is the starting material.

It is not science-based since, by its very nature, it is market-based. Further, there is no scientific rationale presented to justify the market-based approach. A presentation of the Agency's rationale for the scientific basis of the market-based criterion would be most helpful to allow its analysis and feedback by Industry.

Science-based criteria for requiring differing documentation for a SMC and to determine whether the SMC is, in fact, the starting material or API Starting Material (APISM) are suggested below. The key issues are whether the Applicant (i.e. sponsor of the (A)NDA):

1. ...has been informed of the synthetic route of the SMC by its manufacturer or has learned of it by some other credible means; or,

2. ...has an agreement with the manufacturer of the SMC to inform of any changes that would be transparent to the Applicant. Usually these are scale, equipment and process changes but may also include specification, site and a change of manufacturer itself. The latter three are usually not transparent but are included here for completeness sake; or

3. Whether the SMC is commercially available. The latter term is used here as per the classic definition found in the 1987 Guidance. Although this Draft does not use the term, it could well do so, since it defines classic commercial availability very well in lines 1886-1893. Therefore, the term should still be regarded as relevant and remains useful.

The above three items are more appropriate criteria than the market-based one for the following reasons:

Knowledge of the synthetic route (Item #1) is the science-based lynchpin and allows the Applicant to develop adequate specifications and relevant analytical methods for the SMC. Knowing the synthesis, the identity of its precursors are also known and, further, potential impurities beyond those actually found in batches can be postulated and independently synthesized, thereby allowing the specificity of the analytical methods developed to reflect this additional knowledge. Armed with these specifications and methods, the Applicant is able to detect changes in both the overall purity and impurity profile of the SMC. This prevents the manufacturer of the SMC from making significant changes and those changes being transparent to the Applicant, since they will affect either the overall purity and/or the fingerprint impurity profile of the SMC.

Obtaining an agreement with the manufacturer of the SMC (Item #2) is necessary if the synthesis is not known but is a nice insurance policy to have even if the synthesis is known. However, in any case, it may be very difficult to obtain. The manufacturer may have little incentive to cooperate or intellectual property issues may prevent revelation of the information.

Classic commercial availability (Item #3) reiterates that historically the Agency has been quite willing to allow commercially available materials to be defined as the APISM, whether or not the synthesis was known, provided specifications were met. This Draft Guidance proposes more stringent specification requirements that allow the use of commercially available material as APISMs and still provide the desired protection required due to FDA's limited oversight of the APISM's synthesis.

The above rationale can be summarized in the attached decision tree (see page 9) which is offered as an alternative to the approach taken by this Draft to determine both the level of documentation required and whether the SMC is defendable as the APISM.

The Decision Tree asks only the critical questions of the SMC as discussed above and, depending on the answers, an Applicant either meets just the specification requirement or both the specification and selection principle requirement. (However see items # 5, 6 and 7 below.) Although no market

characteristics of the SMC are considered, the approach leads directly to a science-based conclusion as to whether the SMC is the APISM and thereby the level of documentation required to support this conclusion.

This approach, as does the Draft's, also makes it unnecessary to discuss whether the APISM is being made in-house or by an outside contractor since, once defined, the synthesis of the APISM is outside the GMP umbrella, regardless of the site of manufacture.

The approach assumes that the SMC meets the elementary requirement of an APISM, namely, that it contributes to the structure of the API itself.

2. There is no scientific or regulatory basis for requiring the Applicant to begin the flow diagram and document the process details of a synthesis prior to the proposed APISM, i.e., back to the starting material. This is the Draft's requirement for a SMC without a significant NPM (lines 1834-1836).

Information prior to the APISM is outside the GMP umbrella and should therefore not be the subject of either a filing or an inspection. The requirements of the Field and Center are compatible enough so as not to ask for one version of a flow diagram/process details of a synthesis for the Center and another for the Field. This will cause inspectional confusion for both the inspectors and the inspected since non-GMP and GMP synthetic information will both be in the filing. Further, it flies in the face of the Agency's efforts to comply with its own Initiative for the 21st Century wherein *less* information is requested to be filed, rather than more. It demonstrates a complete disconnect with the approach strongly implied in Q7A, wherein documentation begins at the APISM, not before. Subsequent guidelines from FDA should not and need not contradict this important, internationally accepted aspect of the GMP guidance for APIs to which FDA itself had such strong input. The Draft, unfortunately, ignores an excellent opportunity to more fully discuss how its treatment of the starting material issue complements, but does not contradict, Q7A's guidance. (Note, however, the above exception!) This discussion would make clear that the Draft is completely supportive of one objective of the Agency's Initiative for the 21st Century, namely, better coordination between the Field (Q7A) and the Center (this Draft) on this issue. Hopefully, the Agency will take advantage of this opportunity and include this discussion in the approved Guidance.

Further, Industry will, when possible, respond in various levels of detail to this requirement; some more detailed than others. Some will include reagents, some detailed reaction conditions etc; some won't. From experience, I can predict that soon Industry will be asking the Agency for an additional guideline defining the level of detail necessary to document the part of a synthesis that is not even GMP! Soon thereafter, Industry will ask for a quasi-GMP system to be developed by which these molecules outside the GMP umbrella need be synthesized. And so the documentation will grow and grow and grow.

Even in the biological arena (Attachment II), there is no reason to begin the process documentation prior to the APISM, which, in this case, is usually a plant or animal extract. The Agency certainly needs information on the plant or animal starting material as is indicated in lines 2029-2053. But to require the documentation (lines 2057-2065) to depict the process from the starting material to the APISM, is again asking for process detail outside the GMP umbrella.

This requirement also contradicts lines 688-689 of the Draft itself wherein it is stated that the starting material and APISM should, in general, be the same for a synthetic drug substance.

Finally, this requirement is problematic since, if the APISM without a NPM is outsourced or purchased, its preparative information may not be obtainable by the Applicant either because of intellectual property issues or just a lack of cooperation on the part of the manufacturer.

The philosophy that the documentation for a filing needs to be fundamentally different than the documentation reviewed during an inspection is fallacious. It is true that there are some differences (SOPs, process validation information, etc) but the significant area of overlap is no better seen than in the Type II DMF itself. This is an extensively used document during an inspection and yet its format and content needs to be the same as the CMC section of an IND and/or (A) NDA! It is both a filing and inspectional document, demonstrating the significant overlap of both the Center and the Field's responsibilities.

3. The term "API Starting Material" should be added to the Glossary. This would afford the Agency the opportunity to state the important differences between this term and the term "starting material." This is discussed in the

text of the Draft (lines 683-691), but is too important not to also be included in the Glossary. It would be most beneficial to include it as further clarification to the definition of "starting material" (lines 2234-2239).

In addition, terms such as "reagent, catalyst and raw materials" should also be defined in the Glossary, since they need to be clearly differentiated from the above two terms.

4. Lines 1683-1685 state that a drug substance cannot be the APISM for another API. In the absence of a Type II DMF reference that is understandable and justifiable. However, there are cases where a DMF reference can be provided. In that case, although the drug substance would still not be the APISM, the flow diagram in the (A)NDA could begin with the API, accompanied by the DMF reference. This scenario deserves further discussion / clarification.

5. Although there is much merit in the Specification requirement (lines 1843-1867), it mimics too closely that of the drug substance itself. Justifiably, the Draft teaches that the APISM needs rigorous specifications that essentially serve to protect the API from FDA's limited oversight of the APISM's preparation. However, making APISM specifications virtually identical to API specifications removes all distinction (specification-wise) between the APISM and the API itself. This is overkill guidance, i.e., a disproportional response.

   Requiring limits on individual organic impurities at a 0.1% threshold is a case in point (line 1860). It would seem a 0.3% threshold would suffice to afford the needed protection and yet provide a reasonable differentiation between the APISM and the API itself.

   The section should make clear that where process development work has demonstrated that there is no carryover of impurities, the NMT 0.1% limit on unspecified impurities (lines 1860-1861) limit is unnecessary. Alternatively, process development work may even justify a higher limit.

   Note the arbitrary extension of the threshold to 0.2% for veterinary materials, indicates that there is flexibility in this area (lines 1862-1863).

6. The Carryover selection principle (lines 1775-1797) has much merit as well. Except, here again, it is too quantitatively rigorous. Presently there are no

restrictions on carryover and, in general, APISMs are being reasonably defined. To go from no restrictions to a restriction of 0.1 %, seems extreme (line 1785). As long as the APISM has adequate specifications and relevant analytical methods, it should not be problematic to have carryover somewhere in the 0.2-0.4 % range and still allow the SMC to be the APISM. After all, impurities, specified or unspecified, in the API are qualified and therefore, regardless of level or origin, do not present a safety or efficacy issue.

Note the arbitrary extension of the threshold to 0.2% for veterinary materials, indicates that there is flexibility in this area (lines 1785-1786).

7. The Complexity selection principle: The criteria proposed to define the term "readily distinguishable" (IR, UV and Visible spectrometry , lines 1812-1814) and the examples given of "advanced techniques" (1815-1816) are inappropriate. NMR, chiral and achiral HPLC and other chromatographic methods are now routine tools and should be included with spectroscopy. An example: 7-Amino cephalosporanic acid (7-ACA; APISM for most of the cephalosporin antibiotics) is essentially a commodity item today; commercially available in the classic 1987 Guidance sense as well as the sense of this Draft. One cannot differentiate its four isomers just by the use of IR, UV or Visible spectroscopy, yet it meets all the other criteria for being an APISM.

   Further, the issue should not be whether the isomers are "readily distinguishable." They simply need to be distinguishable by whatever the analytical science of the day can bring to the Table. Disqualification based on this principal is justified only if the SMC contains too many of these complex structural elements, as stated in lines 1807 and 1808.

8. Defining the APISM at the end of Phase II is usually too late. Significant dollars are spent on outsourcing or manufacturing drug substances or intermediates in-house, prior to the end of Phase II. Not knowing the identity of the APISM prevents outsourcing to non-GMPs firms (or GMP firms with a non-GMP site), since one is never sure if the Applicant's choice of the APISM will be accepted by FDA. So one errs on the side of caution and costs increase considerably. Identification of the APISM should be clarified at the IND submission, with the Applicant making its case then. The only downside is the possibility that the synthetic route will be changed. However, this is a risk the Applicant would gladly take, in exchange for the

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assurance that the APISM is known at this stage of the developmental pipeline. FDA should be open to meetings to discuss this issue throughout the entire IND to NDA development pipeline.

I hope the above comments are useful and look forward to issuance of the final guidance.

Regards,

Arthur Fabian, Ph.D
Executive Director, Technical Affairs
email: afabian@sst-corp.com

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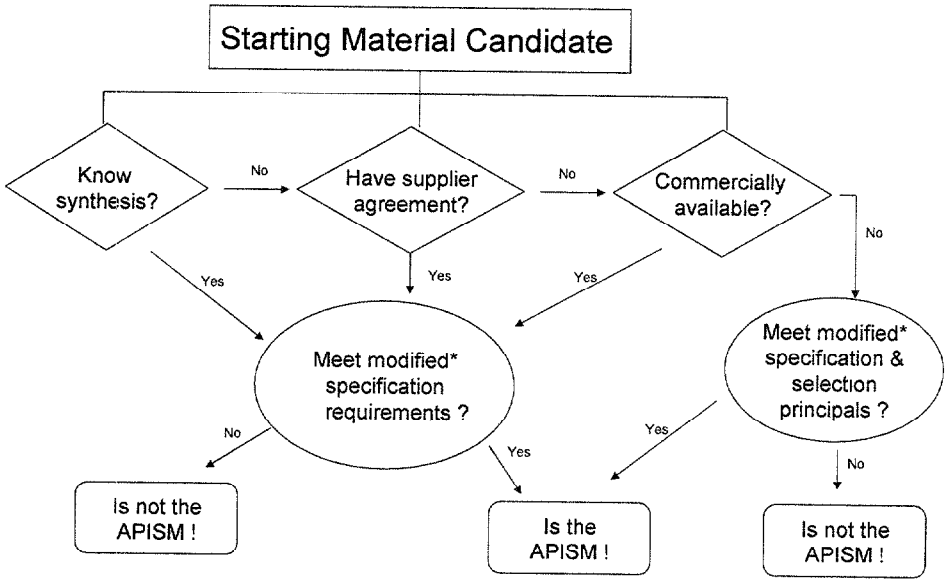
Alternate Proposal A Fabian/SST Corporation



* Modified as per items #5,6,7 of Cover Letter